Applicant thanks Examiners Lambertson and Leffers for conducting a personal interview with Applicant's representative on April 30, 2003. As recorded in the Interview Summary, the rejection of claims 88-91 under 35 U.S.C. §102(e) were discussed. The remarks below are believed by Applicant to substantially conform to the issues discussed in the personal interview.

Claims 88-91 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by United States Patent No. 5,403,484, to Ladner et al.

For a publication to anticipate a claimed invention the disclosure of the publication must be enabled. "[E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *In re Borst*, 345 F.2d 851, 855, 145 U.S.P.Q. 554, 557 (C.C.P.A. 1965), *cert. denied*, 382 U.S. 973, 148 U.S.P.Q. 771 (1966). A reference which merely describes a thing or a process without telling how to make it or carry it out does not support a holding of anticipation. *In re Legrice*, 301 F.2d 929, 936, 133 U.S.P.Q. 365, __ (1962). Rather, for the enablement requirement to be met met the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *Genentech, Inc. v. Novo Nodisk A/S*, 108 F.3d 1361, 1365, 42 U.S.P.Q.2d 1001, 1004 (Fed. Cir. 1997); *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360-61, 47 U.S.P.Q.2d 1705, __ (Fed. Cir. 1998); *Plant Genetics Systems, N.V. v. Dekalb Genetics Corp.*, 315 F.3d 1335, 1339, 65 U.S.P.Q.2d 1452, __ (Fed. Cir. 2003). Moreover, a patent must be enabled as

of its filing date. *Plant Genetics Systems*, 315 F.3d at 1340-41, 65 U.S.P.Q.2d at __.

In view of the above-recited decisions of the Federal Circuit, Applicant contends that in regard to the fusion proteins of claims 88-91, Ladner et al. does not provide reasonable guidance as to how to make and use gene VIII containing fusion proteins without undue experimentation. Without conceding that Ladner et al. is enabled as of its last continuation-in-part (CIP) filing date of March 1, 1991, Applicant wishes to point out that Ladner et al. has an intermediate CIP filing date of March 2, 1990. With regard to the specification having this intermediate date of March 2, 1990, Applicant contends lack of enablement for the gene VIII fusion proteins allegedly described in both U.S. Patent Nos. 5,223,409 (the `409 patent) and 5,403,484 (the `484 patent) and claimed in the `484 patent. Failure to enable the gene VIII fusion proteins at least as early as the CIP filing date of March 2, 1990, precludes the benefit of priority to this date and renders Ladner et al. inapplicable as prior art to the invention of claims 88-91 in the above-identified application.

In this regard, the description within the March 2, 1990 CIP application (the `063 application) is based on mere speculation and conflicting reports by others in the art. As described further below, it is apparent by the description within the `063 application that Ladner et al. simply took the description of the originally filed parent application and added a discussion of the then current literature. Such a discussion

includes concerns by those skilled in the art which are both for and against the substitution of a heterologous leader sequence. Ladner et al. appears to indicate his own concerns by drafting prophetic examples for the substitution of three different leader sequences. The actual secretion of any resultant fusion protein using these heterologous signal sequences was never tested. Ladner et al. does not provide adequate guidance as how to make and use the described gene VIII fusions because there were contentions in the art as to what fusion protein structure would work, if at all, which the '063 application does not resolve. Therefore, Ladner et al. lacks guidance as to the predictability of whether a gene VIII fusion protein would work as well as what would be the structure of such a gene VIII fusion protein. Accordingly, Ladner et al., at most, simply provides an invitation to experiment.

In support of this contention, Applicant presents the following evidence.

First, the parent application, serial no. 07/240,160, filed September 2, 1988 (the '160 application) was filed with a single prophetic example directed to gene VIII surface expression. The specification actually states that the example is hypothetical. Attached for the Examiner's convenience as Exhibit 1 is page 174 of the '160 application wherein lines 6 and 16 state that the Example is hypothetical. Inspection of the text throughout the remainder of this single Example further supports that the entire description is hypothetical.

Further, the '160 application acknowledges that it is unknown whether the gene VIII fusion proteins will work as described since on page 205, lines 15-21 it discusses different alternatives which can be tried if "none of the described approaches produces a working chimeric protein" (attached as Exhibit 2). Thus, the description of working chimeric gene VIII fusion proteins is simply speculation in the '160 application.

Second, the speculative descriptions directed toward the predictability of working gene VIII fusion proteins are not solved by the subsequent filing of the '063 CIP application. This subsequent continuation-in-part application, serial no. 07/487,063 (the '063 application) was filed March 2, 1990, and contains added descriptions to possible alternatives for fusion protein production. However, it is absent of any further reliable information over the '160 application for the successful production of gene VIII fusion proteins in a predictable manner.

For example, Exhibit 2 which is taken from the '160 application, hypothesizes that a different signal sequence may be tried to produce a working chimeric protein or to use a different outer surface protein (OSP) such as gene III since there is fusion data for that gene. Example I of the '063 application simply carries forward these same hypotheses. For example, Exhibits 3 and 4, page 186, lines 11-18 and page 188, lines 15-25, respectively, again state that no fusions of gene VIII have been reported to other genes and that different signal sequences may be attempted should direct fusion of BPTI to M13 CP fail to cause surface expression. Exhibit 4 also summarizes

other manipulations which could be attempted in an effort to successfully achieve surface expression of gene VIII fusion proteins. Applicant asserts that such descriptions cannot be viewed as guidance which would enable one skilled in the art to practice the invention because they are speculative and teach a desire to achieve a goal rather than a predictable method or structure that will work. Accordingly, such descriptions provide nothing more than an invitation to experiment and would lead one skilled in the art to conclude that, at the time the '063 application was filed, undue experimentation would be required to make and use gene VIII fusion proteins as disclosed in the '063 application.

Third, the descriptions within the '063 application regarding successful surface expression of gene VIII fusion proteins are inconsistent and contradictory. For example, with the addition of the language discussed in Exhibit 3, the '063 application still maintains the entire hypothetical example alleging that gene VIII surface expression works using the wild type gene VIII signal sequence.

Exhibit 5, pages 199-201 of the '063 application is an example of such teachings. On page 199, lines 30-32, the '063 application states that the description of the gene set forth therein will cause the surface expression of BPTI. The construct consists of BBTI inserted in gene VIII between the signal sequence and the mature coat protein. On page 200, lines 4-6, and page 201, lines 4-6, these descriptions state that signal peptidase will cleave the chimeric coat protein after the signal

sequence and that the chimeric gene is expressed and processed in parallel with the wild type gene VIII. However, these descriptions are inaccurate and inconsistent with what is taught latter in new Example 2 of the '063 application.

The new Example teaches that the use of gene VIII signal sequence does not work. Example 2 is stated to involve the display of BPTI as a fusion to mature gene VIII coat protein. First described is again the use of the gene VIII signal sequence to achieve surface expression (see Exhibit 6, page 246, lines 10-17). In contrast to what is taught in the previous Example, the new Example teaches that the gene VIII signal sequence does not work. Attached as Exhibit 7 is page 251 of the '063 application where lines 37-40 state that "... no processed protein could be seen on phage or in cell extracts ...". The above descriptions expressly conflict such that one skilled in the art would doubt the reliability of the application's teachings as of the filing date of the '063 application.

The '063 application goes further and additionally contradicts its new description alleging data that the gene VIII signal sequence actually works, albeit at reduced levels. Attached as Exhibit 8, is Table 108 of the '063 application where line 10 describes that the gene VIII signal sequence produces a fusion protein that is "weakly present" on the surface. Thus, within the new matter added to the '063 CIP application, one description states that "no processed gene VIII protein" could be detected (Exhibit 7) while another description alleges it to be present (Exhibit 8).

The cumulation of speculative descriptions, express statements that gene VIII fusion proteins do not work, inaccurate and contradictory statements can only leave one skilled in the art to question what does Ladner et al. actually teach? Does gene VIII fusion protein expression work? Does it work with a gene VIII sequence? Further, if the gene VIII signal sequence doesn't work, then what signal sequence, if any, will work? Thus, Applicant asserts that these speculative and contradictory teachings within the same application cannot provide adequate guidance which would allow one skilled in the art to produce gene VIII fusion proteins without undue experimentation.

Further in regard to a lack of adequate guidance, those skilled in the art would assume that if Ladner et al. were confident that expression with a gene VIII signal sequence did not work then he would have removed the hypothetical description of this alternative at the time the '063 application was filed. Such was the case in the second filed continuation-in-part application, serial no. 07/664,989, filed March 1, 1991, and issued as U.S. Patent 5,223,409 (the '409 patent). In this later filed continuation-in-part application, all descriptions related to "successful" expression of gene VIII fusion proteins utilizing the gene VIII signal sequence was removed. Instead, only the descriptions directed to the fact that this signal sequence <u>will not work</u> is retained. Those skilled in the art can only conclude by the inaccuracies and inconsistencies found in the '063 application and by the abrupt deletion of speculative and contradictory subject matter in the later filed '409 patent that Ladner et al. did not know whether the gene VIII fusion protein

expression actually worked or not at the time the `063 application was filed. Such inaccuracies and inconsistancies show an extreme lack of predictability as to how to practice the invention without undue experimentation and cannot be viewed as enabling.

Fourth, the description within the '063 application to the production of the gene VIII fusion protein using signal sequences other than gene VIII similarly lacks adequate guidance in light of the previous teachings within the application. For example, there is a speculative description in Example I offering possibilities of other signal sequences to attempt if the gene VIII signal does not work and then there is an alleged description of the use of these other signal sequences. Exhibit 9, pages 257-260 of the '063 application describe this use and alleges that these other signal sequences work. For example, page 259, first paragraph, concludes that there are "interesting" proteins that appear to migrate at a site consistent with the fully processed form and refers to Table 108 (Exhibit 8).

Those skilled in the art would question whether the above results in Exhibit 9 are reliable and accurate. As described above, the '063 application had previously presented contradictory results regarding gene VIII signal sequences. Why would results regarding the use of other signal sequences be any less contradictory and be viewed as more reliable to one skilled in the art? Moreover, by retaining the speculative alternatives pertaining to what may be done to achieve surface expression, one

skilled in the art would likely question whether the one alternative signal sequence actually worked as described.

Moreover, the '063 application appears to be misleading in its description of successfully processed gene VIII fusion proteins because there is no explicit description of which of the many gene constructs actually worked (page 259 of Exhibit 9). Reference is made to Table 108 to show the results of surface expression. However, this Table raises further inconsistencies. First, the descriptions of gene VIII fusion proteins using a gene VIII signal sequence are contradictory (described previously). And second, Table 108 appears misleading in that page 259 of Exhibit 9 presents a summary of various signal peptide variants whereas Table 108 only describes the phoA variant. The question arises as to why the description of these results on page 259 appear to imply that more than one variant was actually assayed? These inconsistencies, especially in light of the previous contradictions, leave one skilled in the art with the obvious questions as to which variants were actually constructed? Which variants were actually assayed? And what were the actual results for any or all of these variants?

Finally, the results described in the `063 application are contradictory and inconsistent with the results corresponding to this work published in a scientific peer reviewed journal. Attached as Exhibit 10 is an article published by Markland et al. This publication describes substantially the same results as that described in the `409 patent and was submitted for publication after the filing date of the `409 patent. The senior author on

this publication is Ladner. The article describes that it was considered feasible for the gene VIII signal peptide to function (page 14, first column, last sentence of the third paragraph) but the results obtained show that the protein product was not being processed to yield a mature gene VIII fusion protein (page 15, first column, end of first paragraph). The results reported in this article are consistent only with the specification of the `409 patent since there is no description of a working gene VIII signal sequence. Therefore, by retaining the Example to successful gene VIII fusion protein production utilizing a gene VIII signal sequence in the `063 application, those skilled in the art must conclude that, at the time of filing, Ladner was still considering whether it worked or not. Had Ladner actually known, the description of successful gene VIII signal sequence utilization would have been removed as was done in the `409 patent and in the publication Markland et al.

In regard to inconsistencies, the actual expression data in Markland et al. of the signal sequence variants appears not to correlate with their qualitative description presented in Table 108. The Markland et al. article shows the actual expression levels of the signal sequence variants presented in Table 108 of the `063 application (Exhibit 8). Table 108 of the `063 application qualitatively represents the expression levels as a series of pluses and minuses. A key to the plus and minus symbols is shown on lines 25-29 of the Table legend where "+++" represents very strong presence of either the processed (13 kd) or unprocessed (16 kd) forms. The gene VIII results presented in line 10 of the Table correspond to the duplicates in lanes 9 and

10 of Figure 2 in the Markland et al. article. Similarly, line 11 from Table 108 corresponds to the duplicates in lanes 5 and 6, whereas line 15 of Table 108 corresponds to the duplicates in lanes 12 and 13.

Inspection of the actual data and comparison to Table 108 in the `063 application reveals several inconsistencies. First, the MB42 construct is shown by a "+" to be processed in line 11 of Table 108. Figure 2, lanes 5 and 6 of Markland et al. do not appear to show any such processed species. Second, the alleged processed species shown by a "+/-" in line 10 is inconclusive based on the data shown in lanes 9 and 10. A lower molecular weight band exists in these lanes however they do not appear to be of the same molecular weight as the apparently processed form shown in adjacent lanes 12 and 13. There are no markers to actually determine the molecular weight of this species either. Based on these observations, it is equally likely that the lower band represents a degradation product of the unprocessed species. Finally, the '063 application determines that the 13 kd species described in line 15 is equally present as the 16 kd species described in line 10 of Table 108 since both are denoted by "+++". Inspection of the corresponding lanes in Figure 2 of Markland et al. does not yield similar conclusions. The 13 kd species in lanes 12 and 13 appear to be much less abundant than the 16 kd species in lanes 9 and 10. These results raise again the obvious questions as to whether Ladner actually knew any of his results at the time the `063 application was filed. Other inconsistencies between the actual

data published in the Markland et al. article and that presented in the `063 application exist as well.

Based on all of the above, Applicant concludes that the surface expression of gene VIII fusion proteins, with or without, signal sequence variants was not enabled at the time the `063 application was filed. It wasn't until the filing of the second continuation-in-part application, the `409 patent, that Ladner et al. was able to remove hypothetical and speculative descriptions of possible alternatives for producing working gene VIII fusion proteins. It wasn't until after that filing did Ladner et al. submit a scientific article for publication, the data of which appears to contradict the results of the earlier filed `063 application.

Applicant, on the other hand, describes and claims gene VIII fusion proteins that can be expressed on the surface of a filamentous bacteriophage from a compatible host cell. In light of the inability of the '063 application to provide sufficient teachings for one skilled in the art to express gene VIII fusion proteins without undue experimentation as of its filing date of March 2, 1990, the cited '409 patent cannot anticipate claims 88-91 because it was not enabled prior to Applicant's priority date of September 28, 1990. *In re Borst*, 345 F.2d at 855, 145 U.S.P.Q. at 557 (*accord Minnesota Mining and Manufacturing, Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301, 1306, 65 U.S.P.Q.2d 1270 (Fed. Cir. 2002)). Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) be removed.

Obviousness-Type Double Patenting

Claim 1 stands rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 29 of U.S. Patent No. 6,258,530.

Clam 1 stands rejected under the judicially created doctrine of obviousness-type double patenting as allegedly obvious over claims 1 and 29 of U.S. Patent No. 6,258,530 (`530 patent).

Applicant contends that claim 1 is unobvious in light of claims 1 and 29 of the `530 patent. Claim 1 of the above-identified application is directed to a plurality of cells containing a diverse population of expressible oligonucleotides having a desirable bias of random codon sequences produced from random combinations of first and second oligonucleotide precursor populations.

In contrast, claim 1 of the `530 patent is directed a plurality of cells where oligonucleotides are linked to a suppressible stop codon and to the major coat protein of a filamentous bacteriophage and where expression elements direct the expression of oligonucleotides from a filamentous bacteriophage vector as a major coat protein fusion in a suppressor host or as a soluble peptide in a non-suppressor host. Claim 29 of the `530 patent is directed to a population of oligonucleotides encoding completely random amino acid sequences. Applicant contends that claims 1 and 29 of the `530 patent do not

render claim 1 of the instant application obvious because claims 1 of the `530 patent is directed to particular and distinct modes of expression that result in alternative expression of a peptide when used in conjunction with specific types of procaryotic host cells. Accordingly, it would not be obvious to one skilled in the art to produce a plurality of cells as claimed in the instant application in light of the particularities of claims 1 and 29 in the `530 application. Applicant therefore, respectfully requests that this ground of rejection be removed.

CONCLUSION

In light of the Remarks herein, Applicant submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned.

Respectfully submitted,

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